Synthesis of Isoquinolines. VIII. 3,4,11,11a-Tetrahydro-1H-benzo[*b*]quinolizin-2(6H)-ones[1]

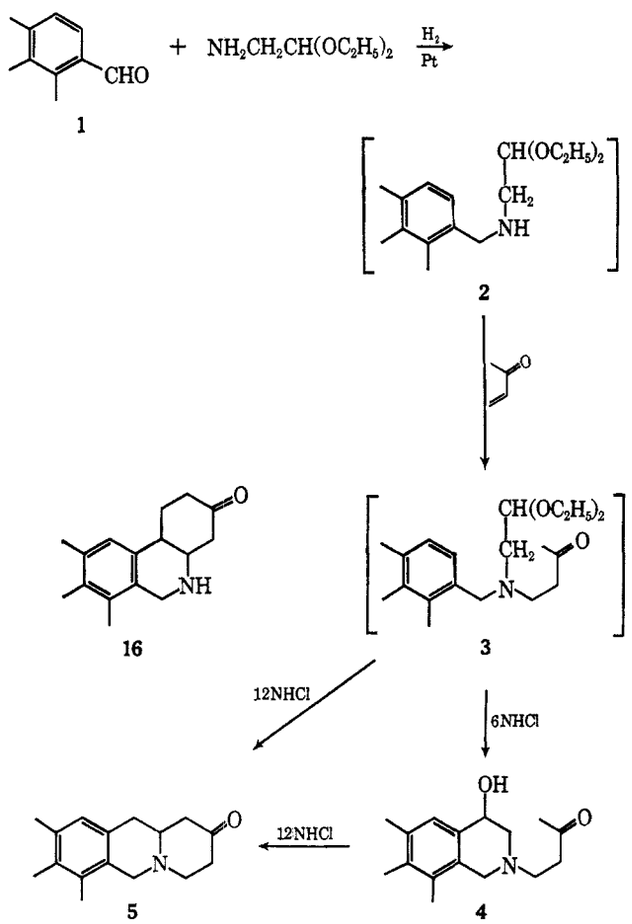
J. M. BOBBITT AND T. E. MOORE[2]

Department of Chemistry, The University of Connecticut, Storrs, Connecticut

Received January 2, 1968

In the past few years we have been able to develop a new and facile synthesis of a number of oxygenated isoquinolines.[3] In at least one of these reaction schemes (leading to 4-benzylisoquinolines[4]) the reactions appear to take place through an intermediate 1,2-dihydroisoquinoline. The 1,2-dihydroisoquinolines are susceptible to nucleophilic attack at position 3 and to electrophilic attack at position 4.[4,5] We have now incorporated the reactivity of position 3 into our general methods and have developed the synthesis shown in the reaction scheme for the preparation of 3,4,11,-11a-tetrahydro-1H-benzo[*b*]quinolizin-2(6H)-ones.

The syntheses and stereochemistry of a series of derivatives of 3,4,11,11a-tetrahydro-2H-benzo[*b*]quinolizin-1-(6H)-one has been recently studied by Kupchan and DeGrazia.[6]



The benzylaminoacetaldehyde acetals **2** were prepared by our previous methods[7] and allowed to react with methyl vinyl ketone to yield the addition products **3**. These addition products, on treatment with 6 *N* hydrochloric acid, cyclized to yield the N-substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**4**).[1] The specific compounds obtained and their yields are recorded in Table I. The yields are over-all yields (**1** → **3** → **4**). When either **3** or **4** was treated with 12 *N* hydrochloric acid, the tricyclic ketones (**5**) resulted. The specific compounds obtained and the yields are recorded in Table II. The yields are over-all yields (**1** → **3** → **5**) and were slightly erratic. In none of the reactions was there any evidence for alternate ring closure (*ortho* rather than *para*, for example in the synthesis of **6**, **7**, or **10**).

The structure proof of compounds **6–15** is based upon their mode of formation, their elemental analyses, their ir spectra, and their nmr spectra. The methyl singlet in the nmr spectra of **4** appeared in the range of τ 7.7–7.8 and was absent in **5**. The spectra of **4** were similar to those of the 4-hydroxy-1,2,3,4-tetrahydroisoquinolines previously reported.[1] The aromatic protons appeared as predicted. The various other protons appeared as unresolvable patterns in the region τ 7.1–7.5. The members of the series had nearly identical spectra in this region.

The isomeric structure (**16**) could also result from the ring-closure reaction if the methyl vinyl ketone had come off during the reaction and condensed at the 3,4 positions. However, the ir spectrum of **15** (having no phenolic hydrogens), in solution, showed the complete absence of any N–H adsorption. This conclusion can be extrapolated to the other members of the series through the similar nmr spectra.

Experimental Section[8]

N-(3-Oxobutyl)-4-hydroxy-1,2,3,4-tetrahydroisoquinolines (4). General Procedure.—Substituted N-benzylaminoacetaldehyde diethyl acetals **2** were prepared from the appropriate benzaldehydes **1** in 0.02-mol quantities by a general procedure already described.[7] The oily bases were dissolved in 5 ml of ether and covered with a nitrogen atmosphere. Methyl vinyl ketone (0.02 mol, 1.4 g) was added and the solutions were allowed to stand at room temperature from 10 to 26 hr. The time required for each compound was determined by tlc (ether–methanol, 6:1, on silica gel G). The ether was evaporated on a rotary vacuum evaporator and the residual oil was treated with 60 ml of cold 6 *N* hydrochloric acid. The acid solution was then washed three times with 30-ml portions of a 3:2 mixture of ether–benzene and allowed to stand at room temperature for 10–18 hr. The acid solution was cooled in an ice bath and made basic with aqueous ammonia. The free amine was extracted from the aqueous solution with several portions of chloroform and the chloroform extracts were combined and concentrated on a rotary vacuum evaporator. At this point the addition of ethanol to **6**, **7**, and **8** gave crystals. Methanol was added to crystallize compound **9**. The products were collected by filtration. The general procedure is valid with the following exceptions: the acid solution of **7** was heated at 45–50° for 0.5 hr after extracting it with ether–benzene; and compound **10** was obtained as a hydrochloride after concentration of the acid solution under vacuum and precipitation with ethanol. Compounds **6** and **7**

(1) Paper VII: J. M. Bobbitt and J. C. Sih, *J. Org. Chem.*, **33**, 856 (1968).

(2) (a) National Aeronautics and Space Agency Fellowship recipient. (b) Abstracted in part from the Ph.D. Thesis of T. E. M., The University of Connecticut, 1968.

(3) See ref 1 and the preceding papers of this series.

(4) J. M. Bobbitt, D. P. Winter, and J. M. Kiely, *J. Org. Chem.*, **30**, 2459 (1965).

(5) A. R. Battersby and R. Binks, *J. Chem. Soc.*, 2888 (1955); C. Schöpf, G. Herbert, R. Rausch, and G. Schröder, *Angew. Chem.*, **69**, 391 (1957).

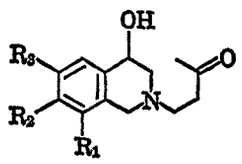
(6) S. M. Kupchan and C. G. DeGrazia, *J. Org. Chem.*, **31**, 1716 (1966).

(7) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *ibid.*, **30**, 2247 (1965).

(8) All melting points were taken on a Thomas–Hoover apparatus and are corrected. The nmr spectra were measured on a Varian A-60 instrument and the shifts are measured from tetramethylsilane as an external standard. The microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich, Switzerland.

TABLE I

N-(3-OXOBUTYL)-4-HYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINES

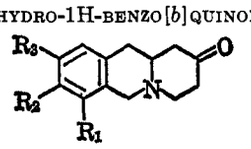


Compd	R_1	R_2	R_3	Yields,[a] %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6	H	OH	OCH_3	51	135–137	63.40	7.17	5.28	63.16	7.26	5.50
7	H	OCH_3	OH	53	138–141	63.40	7.17	5.28	63.12	7.14	5.32
8	H	OCH_3	OCH_3	72	128–128.5	64.50	7.58	5.01	64.41	7.67	5.00
9	OH	OCH_3	H	76	136.5–138.5	63.38	7.22	5.28	63.31	7.22	5.13
10[b]	H	OCH_2O		33	184.5–185.5	56.09	6.06	4.67	56.54	6.22	4.41

[a] Yields are based upon starting aldehydes. [b] Isolated and characterized as hydrochloride salt and as picrate. *Anal.* Calcd: Cl, 11.83. Found: Cl, 11.93.

TABLE II

3,4,11,11a-TETRAHYDRO-1H-BENZO[*b*]QUINOLIZIN-2-(6H)-ONES



Compd	R_1	R_2	R_3	Yield,[a] %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	H	OH	OCH_3	68 (55)	192.5–193.5	68.00	6.93	5.66	68.31	6.86	5.67
12	H	OCH_3	OH	40 (74)	212–213	68.00	6.93	5.66	67.99	6.86	5.65
13	H	OCH_3	OCH_3	66 (22)	140.5–141.5	68.94	7.33	5.36	68.61	7.58	5.29
14	OH	OCH_3	H	60 (59)	163–164	68.00	6.93	5.66	68.10	7.11	5.51
15	H	OCH_2O		41 (79)	168–169	68.56	6.16	5.71	68.69	6.29	5.65

[a] The yields given refer to the sequence 1 → 2 → 3 → 5. The yields in parentheses refer to the conversions of 4 → 5.

were recrystallized from absolute ethanol; **8** was recrystallized from 95% ethanol; **9** was recrystallized from 1-propanol and **10** was recrystallized from methanol. The picrate of **10** was prepared in ethanol from the hydrochloride and recrystallized from methanol to yield an analytical sample, mp 160° dec.

Anal. Calcd for $C_{20}H_{20}N_4O_{11}$: C, 48.81; H, 4.10; N, 11.39. Found: C, 48.73; H, 4.41; N, 11.20.

3,4,11,11a-Tetrahydro-1H-benzo[*b*]quinolizin-2(6H)-ones (5). General Procedure.—The oily tertiary amines (**3**), prepared as described above, were dissolved in 50 ml of concentrated hydrochloric acid. The solutions became hot and were cooled and washed with three portions of a 3:2 mixture of ether–benzene. The acid solutions were then heated at 45–50° for 30 min. The cooled solutions were diluted with water and made basic with aqueous ammonia to pH 9–10. In the cases where the amine did not precipitate at this point (**13** and **14**), the basic, aqueous solution was extracted with chloroform. The chloroform extracts were concentrated to an oil which, when cooled and diluted with a little ethanol, crystallized. The products were collected by filtration. The general procedure is valid with the following exceptions: in the preparation of **13**, the acid solution was heated to 88–95° for 15 min before extracting it with ether–benzene; in the preparation of **14**, the best yields were obtained when the acid solution was allowed to stand at room temperature for about 11 hr instead of heating it. Compounds **12**, **13**, and **15** were recrystallized for analysis from 95% ethanol; **11** was recrystallized from absolute ethanol; and **14** was recrystallized from methanol.

The conditions for the conversion of the 4-hydroxyisoquinolines (**4**) into the tricyclic ketones (**5**) are identical with those given for the conversions of **3** into **5**. The yields are given in parentheses in Table II.

Registry No.—**6**, 16675-64-2; **7**, 16675-65-3; **8**, 16675-66-4; **9**, 16675-67-5; **10** HCl, 16675-68-6; **10** picrate, 16675-69-7; **11**, 16675-70-0; **12**, 16675-72-2; **13**, 16675-71-1; **14**, 16675-73-3; **15**, 16675-74-4.

The Reaction of Piperidoneenamines with Methyl β-Vinylacrylate. A Route to Quinolines and Isoquinolines[1]

S. DANISHEFSKY AND ROBERT CAVANAUGH

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

Received December 21, 1967

Berchtold and Ciabattoni[2] were the first to report on the cycloaddition reaction of enamines with β-vinylacrylic esters. The synthetic importance of this reaction arises from the subsequent retro Michael elimination of the amine function to produce 1,3-cyclohexadienes not otherwise readily preparable.[3] These systems can in turn be aromatized to produce benzene rings.[4] For example, the reaction of the pyrrolidineenamine of cyclopentanone (**1**) and methyl β-vinylacrylate (**2**) affords the fused bicyclic system **3**, which undergoes an elimination reaction to give **4**, which may subsequently be aromatized to **6**. In a concurrent study in this laboratory,[5] the cycloaddition–retro

(1) This research was supported by a grant from the Petroleum Research Fund of the American Chemical Society.

(2) G. A. Berchtold, J. Ciabattoni, and A. A. Tunick, Abstracts, the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 35.

(3) G. A. Berchtold, J. Ciabattoni, and A. A. Tunick, *J. Org. Chem.*, **30**, 3679 (1965).

(4) H. O. House and T. H. Cronin, *ibid.*, **30**, 1061 (1965).

(5) S. Danishefsky and R. Cunningham, *ibid.*, **30**, 3676 (1965).